REMARKS

Claims 245-313 were previously pending in this application. Replacement claims 245, 265, 266, 267 and 275-277 have been entered above. Claims 281 and 285 have been canceled. New claims 314-316 have been added. Accordingly, claims 245-280, 282-284 and 286-316 are presented for further examination on the merits.

Changes to Claims

As indicated above, replacement claims 245, 265, 266, 267 and 275-277 have been entered. As amended, claim 245 is directed to a composition comprising a primary nucleic acid component which upon introduction into a eukaryotic cell produces a secondary nucleic acid component which is capable of producing a nucleic acid product, or a tertiary nucleic acid component, or both, in said eukaryotic cell, wherein said primary nucleic acid component is not obtained with said secondary or tertiary component or said nucleic acid product. Thus, the subject matter of claim 245 specifically covers eukaryotic cells, which was the subject matter of former and now canceled claims 281 and 285, the latter having recited "wherein said cell is eukaryotic or prokaryotic."

Claim 265 has been amended to recite "[a] composition of matter comprising a nucleic acid component which when present in a cell produces a non-natural nucleic acid product, which product comprises (i) a cellular component localizing entity, and (ii) a nucleic acid sequence of interest. As amended, claim 265 now speaks to a *cellular compartment localizing entity*, whereas previously "a portion of a localizing entity" was recited in the claim. To conform with the changes to claim 265, the phrase "portion of the" [localizing entity] has been deleted from claims 266-267 and 275-277 and "cellular compartment" has been added before "localizing entity."

Finally, new claims 314-316 have been added. New claim 314 is directed to a construct which when present in a cell produces a product, the construct being bound non-ionically to an entity comprising a chemical modification or a ligand. In new claim 315, the construct of claim 314 is further defined by having at least one terminus, the terminus comprising a polynucleotide tail. Claim 316 clarifies the polynucleotide tail as being hybridized to a complementary polynucleotide sequence. New claims 314-316 correspond to originally filed claims 22-24. Thus, their entry should not pose any issue of new matter.

Entry of the above amendments and new claims is respectfully requested.

The First Rejection Under 35 U.S.C. 112, 1st Paragraph (Enablement)

Claims 245-313 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the same reasons of record set forth in the Official action mailed 02/16/99. The Examiner's position on enablement is set forth on pages 3-11 in the February 17, 1999 Office Action.

Applicants respectfully traverse the enablement rejection. First, in Applicants view, it would not require undue experimentation for the ordinary skilled artisan to practice the invention. A sufficiently detailed description is provided in the specification for preparing and using the constructs of the present invention, including their entry into eukaryotic cells for expression of sequences for biological function. The description and use of the claimed constructs runs to examples and even figures. Applicants attach hereto a decision tree provided with "Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph-Enablement Chemical/Biotechnical Applications". Two questions are posed in the decision tree. The first is "Does the specification teach how to

make and use at least one embodiment encompassed by the claims as a whole without undue experimentation?" Clearly, the specification has taught one of ordinary skill in the art how to make and use more than one embodiment. The second question is "Are the enabled embodiments representative of the full scope of the claims?" Again the answer is yes. The methods described for obtaining the disclosed constructs could be applied to obtaining any of the constructs encompassed by the pending claims. Therefore, the scope of the present composition claims is deemed appropriate.

It has also been asserted that Applicant does not further address the enablement of the claimed constructs applied to the products which they produce. In the Examiner's view, barriers exist to the successful delivery of antisense to the organism including: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus (2) withstanding enzymatic degradation and (3) the ability to find and bind the target site and simultaneously avoiding non-specific binding. The Office Action cites passages from Branch and Flanagan as evidence of skepticism of those of skill in the art.

In response, Applicants note that Branch and Flanagan were actually published *after* the priority date of the above-referenced application. The MPEP in Section 2164.05(a) states that "the state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date." This section further states "In general, the examiner should not use post-filing date references to demonstrate that the patent is no-enabling." Applicants nevertheless assert that there are a number of publications available as of the priority date of the above-referenced application as well as publications published after the priority date of the above-referenced application which express a more optimistic attitude regarding the suitability of antisense to become useful in therapeutic application. One example of such a publication is Crooke, 1994,

Antisense Research and Development 4:145-6, attached hereto as Exhibit 2. Another example is Liu et al, 1997, J. Virol. 71:4079-4085, attached hereto as Exhibit 3 which discloses Tat-activated expression of chloramphenicol acetyltransferase was shown to be specifically inhibited in cells expressing Tat and transactivation response region antisense sequences.

It is also Applicants' position that *in vivo* data is not necessary. As noted in the MPEP Section 2107.03, III, "Office personnel should be careful not to find evidence unpersuasive simply because no animal model for the human disease condition had been established prior to the filing of the application". However, Applicants do note that clinical trials were being conducted by the assignee of the instant application around its priority date (Exhibit 4). The results have been favorable and a number of public announcements have been made concerning the ongoing clinical trials and results.

Applicants would also like to respond to other points raised in the Office Action. First, as conceded in the Office Action, Applicants have demonstrated the penetration of cells by the antisense compounds, notably antisense inhibition of HIV in infected U937 cell culture. Therefore, the question of penetration of the plasma membrane of target cells should not be an issue.

Second, Applicants note that specificity to any degree and certainly 100% specificity is not required of any drug under the patent laws and is evaluated on a case-by-case basis by the Food and Drug Administration. For example, penicillin is known to be far from specific to a certain target protein of harmful bacteria. This does not diminish, however, the importance of penicillin as a useful drug.

In view of the foregoing remarks and submitted exhibits, Applicants respectfully request reconsideration and withdrawal of the enablement rejection.

The Second Rejection Under 35 U.S.C. §112, 1st Paragraph (Written Description)

Claims 245-289 and 299-313 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the Office Action dated February 19, 2001, the Examiner stated in part:

> The claims broadly encompass "constructs" for producing a "product" and it is not clear what is embraced by the claims.
>
> . . .
>
> Clearly the specification only considers vector-like constructs for delivery and expression of nucleic acids.
>
> . . .
>
> Furthermore, the actual constructs used in the HIV challenge and Lac-Z assays taught in the specification are not described in clear and exact terms (p. 169, line 3 recites "U1 clone", p. 169, para. © recites "triple U1 construct", and p. 167, last line recites "various U1 constructs described above") and it is not clear whether the constructs used had the intron sequence in the T7 polymerase, or even which constructs were used in the assays.
>
> . . .
>
> . . . the specification as filed fails to provide one skilled in the art enough description to show possession of a representative number of "construct" species for the breadth claimed.

Applicants respectfully traverse the rejection. The Final Written Description Guidelines state in Paragraph II.A.3.a.

> Possession may be shown in many ways. For example, possession may be shown, inter alia, by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any

description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. . .

An applicant may show possession of an invention by disclosure of drawings[39] or structural chemical formulas[40] that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. The description need only describe in detail that which is new or not conventional.[41] This is equally true whether the claimed invention is directed to a product or a process.

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

The Written Description Guidelines further state in paragraph II.A.3.a.(2)

(2) For each claim drawn to a genus:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice ....., reduction to drawings ....., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (citation omitted).

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. On the other hand, there may be situations where one species

> adequately supports a genus (citation omitted). What constitutes a "representative number" is an inverse function of the skill and knowledge in the art.
>
> Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus (citation omitted).
>
> Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces (citation omitted). If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 U.S.C. 112, para. 1.

Applicants assert that an adequate description has been provided in the form of a detailed description of the constructs now claimed. The description of the claimed constructs runs to their description in the present specification and even includes working examples and figures.

The disclosures in the specification clearly conform to the Written Description guidelines. Constructs are described in various figures. Applicants note that three cases are cited in footnote 39 pertaining to the use of drawings pertaining to the adequacy of the Written Description Requirement. Specifically, footnote 39 states

> See, e.g., *Vas-Cath*, 935 F.2d at 1565, 19 USPQ2d at 1118 (``drawings alone may provide a `written description' of an invention as required by Sec. 112"); *In re Wolfensperger*, 302 F.2d 950, 133 USPQ 537 (CCPA 1962) (the drawings of applicant's specification provided sufficient written descriptive support for the claim limitation at issue); *Autogiro Co. of America v. United States*, 384 F.2d 391, 398, 155 USPQ 697, 703 (Ct. Cl. 1967) (``In those instances where a visual representation can flesh out words,drawings may be used in the same manner and with the same limitations as the specification.").

Sufficient identifying characteristics of the constructs, compositions and kits of the present invention is provided as noted above in the specification. Additionally, a sufficient number of species have been disclosed. Moreover, the terminology employed by Applicants to describe their constructs (page 169) is accepted in the art, and as such, should be deemed to satisfy the written description test under the law. Finally, Applicants note that actual reduction to practice is not required to satisfy the Written Description Requirement. Footnote 36 of Written Description Guidelines state

> ....."The word 'invention' must refer to a concept that is complete, rather than merely one that is 'substantially complete.' It is true that reduction to practice ordinarily provides the best evidence that an invention is complete. But just because reduction to practice is sufficient evidence of completion, it does not follow that proof of reduction to practice is necessary in very case. Indeed, both the facts of the *Telephone Cases* and the facts of this case demonstrate that one can prove that an invention is complete and ready for patenting before it has actually been reduced to practice.

Therefore, the claimed invention is adequately described.

In view of the above arguments, Applicants assert that the rejection has been overcome. Applicants therefore request that the rejection under 35 U.S.C. 112, first paragraph (written description) be withdrawn.

The Rejections Under 35 U.S.C. §102

Four rejections for anticipation have been lodged against the pending claims. These rejections include the following:

1. Claims 265-298 under 35 U.S.C. §102(e) by Sullinger et al.;
2. Claims 245-249, 251, 255, 258-261 and 264 under 35 U.S.C. §102(b) by Huse et al.;

3. Claims 245-264 and 299-313 under 35 U.S.C. §102(e) by Giri et al.; and

4. Claims 245-313 under 35 U.S.C. §102(b) by De Young et al.

Applicants respectfully traverse all the anticipation rejections and they offer the following remarks in response.

Sullinger et al.

Sullinger does not anticipate the present invention in view of the above amendments to the claims. As set forth in claim 265, Applicants are now claiming a composition of matter comprising a nucleic acid component which when present in a eukaryotic cell produces a non-natural nucleic acid product, which product comprises (i) a cellular compartment localizing entity, and (ii) a nucleic acid sequence of interest. In contrast to the present invention, Sullinger et al. does not localize to a cellular compartment but rather they localize to a viral particle.

Huse et al.

Huse et al. does not anticipate the present invention because their disclosure describes a primary nucleic acid component which produces a secondary nucleic acid component, but lacks Applicants' material element in the form of a tertiary nucleic acid component.

Giri et al.

Giri et al. does not anticipate the present invention in light of the above claim amendments, particularly claim 245. As amended above, claim 245 calls for first, production in a eukaryotic cell, and second, production of a tertiary nucleic acid component in the eukaryotic cell. With respect to claim 299, Giri's disclosure lacks

Applicants' material element, namely, the production of more than one specific nucleic acid sequence. Giri et al. produce but a single nucleic acid sequence, albeit in multiple copies.

De Young et al.

De Young et al. do not anticipate the present invention for the following reason. Although their paper has been characterized for the proposition that "the U1 sequence is a known localizing sequence to the cell nucleus," such is not strictly true. The intact U1 sequence does have localizing properties, but deletions of sequences from the U1 transcript can prevent re-importation of U1 constructs to the nucleus. The present specification explicitly describes designs that preserve this re-importation signal segment. On the other hand, De Young et al. excise out portions that are likely to be involved in the re-importation process. There is no disclosure or suggestion in De Young's paper that re-importation ever took place with their disclosed constructs.

New Claims 314-316

Finally, Although Myers et al. is not cited in the outstanding Office Action, it was cited previously against former and canceled claims 22-24. By the claim amendments above, Applicants have added corresponding claims 314-316. Applicants wish to point out that Myers et al. do not disclose or suggest a construct which when present in a cell produces a product. Instead, Myers et al. disclose an already produced oligonucleotide - but not the production of a product as set forth in new claims 314-316.

Favorable action is respectfully sought.

* * * * * * *

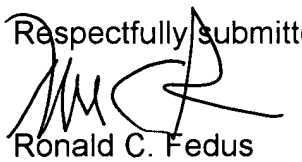
SUMMARY AND CONCLUSIONS

Claims 245-280, 282-284 and 286-316 245-279 are presented for further examination. Three new claims have been added and two claims have been canceled.

No claim fee or other fees are believed due in connection with this response, it being believed that the number of pending claims is less than the highest number of paid claims. In the event that any fee or fees, including claim fees, are due for this paper, or if any other fees are due in connection with this filing, The Patent and Trademark Office is authorized to charge any such fee or fees to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,



Ronald C. Fedus
Registration No. 32,567
Attorney for Applicants

ENZO THERAPEUTICS, INC.
c/o ENZO BIOCHEM, INC.
527 Madison Avenue, 9th Floor
New York, New York 10022
Telephone: (212) 583-0100
Facsimile: (212) 583-0150

MARKED UP VERSION OF THE CLAIMS

245. (Amended) A composition comprising a primary nucleic acid component which upon introduction into a **eukaryotic** cell produces a secondary nucleic acid component which is capable of producing a nucleic acid product, or a tertiary nucleic acid component, or both, **in said eukaryotic cell,** wherein said primary nucleic acid component is not obtained with said secondary or tertiary component or said nucleic acid product.

265. (Amended) A composition of matter comprising a nucleic acid component which when present in a cell produces a non-natural nucleic acid product, which product comprises (i) **[**~~a portion of~~**]** a **cellular component** localizing entity, and (ii) a nucleic acid sequence of interest.

266. (Amended) The composition of claim 265, wherein said **[**~~portion of the~~**]** **cellular compartment** localizing entity (i) is sufficient to permit localization of said non-natural nucleic acid product.

267. (Amended) The composition of claim 265, wherein said **[**~~portion of the~~**]** **cellular compartment** localizing entity (i) comprises a cytoplasmic or nuclear localization signalling sequence.

275. (Amended) The composition of claim 273, wherein said non-natural nucleic acid product comprises antisense RNA or antisense DNA and said **[**~~portion of the~~**]** **cellular compartment** localizing entity (i) comprises a nuclear localization signalling sequence.

276. (Amended) The composition of claim 273, wherein said non-natural nucleic acid product comprises antisense RNA or antisense DNA and said **[**~~portion of the~~**]** **cellular compartment** localizing entity (i) comprises a cytoplasmic localization signalling sequence.

277. (Amended) The composition of claim 273, wherein said non-natural nucleic acid product comprises sense RNA or sense DNA and said **[**~~portion of a~~**]** **cellular compartment** localizing entity (i) comprises a cytoplasmic localization signalling sequence.

* * * * * * *